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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/767,421	01/22/2001	Michael J. Shamblott	JHU1750-1	9551

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LISA A. HAILE, Ph.D.
GRAY CARY WARE & FREIDENRICH LLP
Suite 1100
4365 Executive Drive
San Diego, CA 92121-2133

EXAMINER

CROUCH, DEBORAH

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 05/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/767,421

Applicant(s)

SHAMBLOTT ET AL.

Examiner

Deborah Crouch, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 February 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 and 15-33 is/are pending in the application.
- 4a) Of the above claim(s) 33 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13 and 15-32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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Applicant's arguments filed February 7, 2005 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1-13, 15-33 are pending. Claim 33 has been withdrawn from consideration. Claims 1-13 and 15-32 are examined in this office action.

Support for "serum-free" and "reduced serum" media can be found on page 55 of the specification. Serum-free is regarded by the art as being 0.5% serum or less.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 22-31 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 22 states "reduced serum." However, reduced serum is not defined in the specification nor does it have a clear meaning in the art. The only definition of "reduced serum" in the specification is 5% (page 67, line 6). Applicant needs to point to clear definition of the term so that the metes and bounds are known.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The claims are drawn to a human embryonic body-derived cell culture that comprises cells which do not cause formation of a teratoma when injected into SCID mice and at least

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some of which simultaneously express polypeptide or mRNA markers that are characteristic of at least two different cell types, wherein the cell types are selected from the group consisting of an ectodermal cell, a mesodermal cell and an endodermal cell. The claims are product by process claims: a cell culture derived from human embryoid body cells.

"Derived" in its broadest meaning includes cells that are differentiated from cells isolated from EB's. Further, claim 1 requires that the cells "simultaneously express polypeptide or mRNA markers that are characteristic of at least two cell types." Thus a cell that expresses any one marker that is found on an ectodermal, mesodermal or endodermal cell falls within the scope of the claim. Any cell of the body is ultimately an ectodermal, mesodermal or endodermal cell.

Claims 1-5, 9-13, 15, 16 and 18-20 remain rejected under 35 U.S.C. 102(b) as being clearly anticipated by Allsopp et al (1995) Exper. Cell Res. 219, pp. 130-136 for reasons presented in the office action mailed November 16, 2004.

Allsopp teaches a culture of clonal human fibroblast cells (page 131, col. 1, parag. 2). As claims 1, 3-5, 9-13, 15, 16 and 18-20 encompass the differentiated products of human EB cells, fibroblasts produced by another means anticipate the claims. Further, the fibroblasts of Allsopp would not form teratomas when injected into SCID mice, they simultaneously express nestin mRNA (as evidenced by Jiang) which is a marker of ectodermal, mesodermal and endodermal cells and more than one such marker appears on the surface of the fibroblast, fibroblasts inherently exhibit 30-60 population doublings, proliferate under cell culture conditions that are nonpermissive for proliferation of human embryonic germ cells, proliferate in media lacking LIF and/or a fibroblast feeder layer, are transfectable with a retrovirus or a lentivirus. Whether or not the fibroblasts of Allsopp are derived from tissue sources or from EB cells or a clonal EB cell does not alter the final product.

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Applicant argues that Allsopp does not teach all the limitations of the claims. In particular, applicant argues Allsopp does not teach that the fibroblasts do not form teratomas in SCID mice, express nestin and another marker from ectodermal, mesodermal or endodermal cells, can undergo 30-60 population doublings, proliferate under conditions that are nonpermissive for proliferation of human embryonic germ cells, proliferate in media lacking LIF and/or fibroblast feeder layer and can be transfected with retroviruses or lentiviruses. Applicant argues that Allsopp describes an end-product which is not derived from an embryoid body.

The claims as written encompass a culture of fibroblasts, which have been produced by causing the differentiation of EB-derived cells. Since the EB-derived cells could be differentiated into fibroblasts, the fibroblasts are also EB-derived. There is no evidence on record that fibroblasts produced by differentiation EB's would be different from those of Allsopp. Also, the claims state "at least some of the cells simultaneously". Thus, not all of the cells need to express markers indicative of two of mesodermal, ectodermal or endodermal cells. In fact, the cells don't have to express any such markers in the manner the present claims are written.

While the examiner cannot be sure what applicant is intending to claim, it appears from the specification that the culture is composed of dissociated EB cells, which have the characteristics of as claimed. Applicant is advised, however, any claim amendments after final would probably not be entered because of new search and considerations. Other art may be applicable. Further, each of the characteristics is an inherent feature of fibroblasts. Applicant has not presented any arguments or evidence otherwise.

Claims 1, 6 and 8 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Jin et al. (1993) Differentiation 54, pp. 47-54.

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Jin teaches a culture of clonal human fetal myoblasts (page 49, col. 1, lines 8-10). Jin also teaches that the myoblasts expressed Myf6 (page 50, col. 1, parag. 1, lines 12-17). Myoblasts inherently express nestin, a marker also expressed by neural stem cell. This meets the limitation that the cells express polypeptide or mRNA markers characteristic of two different cell types. Myoblasts are a mesodermal cell and neural stem cells are an ectodermal cell.

Applicant argues that Jin does not teach myoblasts expressing myf6 and nestin from embryoid body derived cells and cell which do not cause teratomas in SCID mice. This argument is not persuasive.

The claims as written encompass a culture of myoblasts, which have been produced by causing the differentiation of EB-derived cells. Since the EB-derived cells could be differentiated into myoblasts, the myoblasts are also EB-derived. There is no evidence on record that myoblasts produced by differentiation EB's would be different from those of Jin. Also, the claims state "at least some of the cells simultaneously" . Thus, not all of the cells need to express markers indicative of two of mesodermal, ectodermal or endodermal cells. In fact, the cells don't have to express any such markers in the manner the present claims are written.

Claims 1 and 7 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Li et al (1996) Cardiovascular Res. 32, 362-373 (new).

Li teaches a culture of human adult and fetal cardiomyocytes, both of which inherently express GATA-4, a marker of cardiac muscle and gastrointestinal tissues composed of, respectively, mesodermal and endodermal cells. Thus, Li clearly anticipates the claim because GATA-4 is s simultaneously expressed in human vascular myocytes and GATA-4 inherently is expressed in mesodermal and endodermal cells.

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Claims 17, 19 and 21 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Damjanov et al (1993) Laboratory Invest. 68, pp 220-232.

Damjanov teaches a human germ cell tumor-derived cell line, which express both valentine and α -fetoprotein (page 222, col. 1, parag. 2, lines 5-6 and Table 1; page 224, figure 6 and page 223, col. 2, lines 1-5). As the cells are transformed, they would inherently proliferate for at least thirty population doublings. A human germ cell line derived from EB cells as encompassed by the claims cannot be distinguished from the human germ cell tumor-derived cell line of Damjanov.

Applicant argues that Damjanov does not teach an embryoid body derived cell which can proliferate for at least 30 population doublings, proliferating in LIF, a fibroblast feeder layer, and transfectable with retrovirus or lenitvirus, and which do not cause teratoma formation. These arguments are not persuasive.

The cells of Damjanov are encompassed by the claims. Further, there is no means to distinguish between the cells of Damjanov and ones differentiated, derived from, EB cells. The characteristics argued by applicant are inherent to the cells of Damjanov. Further it is noted that the claims state proliferating in media lacking LIF. This too is taught by Damjanov, whose cells also proliferated in media lacking LIF.

Claims 1, 11-13 and 15-19 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Lefebvre et al (1998) Diabetes 47, pp. 134-137.

Claims 1, 11-13 and 15-19 contain as an embodiment cells which do not simultaneously express polypeptide or RNA makers that are characteristic of at least two different cell types. These claims state "at least some simultaneously ..."

Lefebvre teaches a culture of human pancreatic islet cells (page 134, col. 2, parag. 1). The markers expressed by human pancreatic islet cells are characteristic of any two of ectodermal, endodermal or mesodermal cells.

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Applicant requests clarification of a typographical error, which is obvious based on each of the previous rejections. However, the examiner will address applicant's predicted rebuttal. The cells of Lefebvre are not distinguishable from human pancreatic islet cells produced by differentiating cells derived from EB's. If one produces a culture of EB cells by dissociating EB's and then differentiates those cells into another cell type, then the differentiated cells are EB derived. As the cells of Lefebvre have the marker composition claimed, they anticipate the claimed invention.

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971), *Northam Warren Corp. v. D. F. Newfield Co.*, 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934) and MPEP 2112.01.

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See, e.g., *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979).

It is noted that applicant has stated that their claims are not product by process claims. This is not persuasive. The claims read as "a cell culture comprising cells produced from human embryoid body cells."

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The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 21-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shamblott in view of Yuen et al. (1998) Blood 91, pp. 3203-3209.

Shamblott teaches the production of a cystic embryoid bodies (EB's) from a culture of cells isolated from human primordial germ (PG) cells (page 13729, col. 1, parag. 1, lines 1-4, parag. 2, lines 1-3 and parag. 1, line 1 to col. 2, line 4). Shamblott further teaches that cells in the EB expressed markers of at least two different cell types such as endodermal and ectodermal markers (page 13729, col. 2, parag. 2). Shamblott teaches that human EG cells behave similarly to mouse ES and EG cells, such as in the formation of EB's, the structure of EB's, the outer layer of the EB's express α -fetoprotein and forming cells of all three germ layers (page 13729, col. 2, parag. 5, lines 3-12).

Yuen teaches the formation of EB's from mouse ES cells, the disaggregation of the EB's and the culture of EB cells in media comprising bFGF, 10% plasma derived serum and ascorbic acid and media comprising 10% fetal calf serum, ascorbic acid, bFGF, VEGF, IGF, and methylcellulose (page 3203, col. 1, parag. 1 and 2). This media is not permissive for EG cells and the media lacks LIF and a fibroblast feeder layer.

While Yuen does not teach the exact media, at the time of filing, optimization of culture conditions to obtain sustained cell growth were well known within the art. Further, the use of human growth factors to culture human PGC cells was taught by Shamblott (page 13727, col. 1, line 10). Also well known within the art at the time of filing, was the use of

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collagen I, human extracellular matrix and treated tissue culture plastic for the growth of stem cells.

The formation of clonal lines of ES cells was well known in the art at the time of filing to develop genetically identical, or nearly so, stem cell lines.

Shamblott teaches that the PG cells disclosed therein had been passaged 25 times, which is about 25 population doublings (page 13730, col. 1, parag. 1, lines 5-7). EG and ES cells were known in the art at the time of filing to be capable of indefinite growth such that 30 population doublings would be an obvious trait of EG and ES cells, or cells from EB's.

Shamblott offers motivation in stating that human pluripotent cells are needed to further define culture conditions and differential gene expression necessary for cell-type-specific differentiation and for the isolation of lineage-restricted stem cells for stem cell therapies (page 13730, col. 1, parag. 2, lines 4-8). The method claimed causes the formation of pluripotent stem cell cultures employing EB formation to increase total cell number. Yuen further offers motivation in demonstrating that EB cells can be differentiated into the hematopoietic lineage (page 3205, col. 2, parag. 1).

Therefore, at the time of filing, it would have been obvious to the ordinary artisan to make a human EBD cell culture as claimed comprising forming EB's, dissociating the EB's and culturing the EB cells under conditions where the cells express markers of more than one cell type as claimed. Sufficient teaching, suggestion and motivation were provided at the time of filing to make and use the invention as presently claimed.

Applicant argues that Shamblott teaches the culture of EB derived cells in DMEM supplemented with 15% FBS, and does not teach the culture in reduced serum or serum free conditions. Applicant argues that Yuen teaches the culture of EB cells the same media as Shamblott and maintained in media supplemented with 10% FCS. Applicant argues that

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neither Shambloott alone nor in combination with Yuen render the claimed invention obvious.

These arguments are not persuasive.

Claims 22 states "serum." Fetal bovine serum meets this limitation. The limitations of reduced serum and serum free are offered in the alternative.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

April 30, 2005